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L8: Entry 21 of 29

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TITLE: Method of treatment of neurodegeneration with calpain inhibitors

Brief Summary Text (15):

Another aspect of the present invention provides a method of inhibiting or treating neurodegeneration in a mammal having or likely to experience a neuropathology. This method includes the administration to the mammal of a therapeutically efficacious amount of Peptide Ketoamide compound that has Calpain inhibitory activity or a pharmaceutically acceptable salt or derivative thereof. This Peptide Ketoamide compound is preferably from one of the following classes: Dipeptide .alpha.-Ketoamides (Subclass A), Dipeptide .alpha.-Ketoamides (Subclass B), Tripeptide .alpha.-Ketoamides, Tetrapeptide .alpha.-Ketoamides and Amino Acid .alpha.-Ketoamides. The method can also include identifying, prior to administration of the compound with Calpain inhibitory activity, a mammal in which neurodegeneration of the CNS is occurring or is likely to occur. The method is useful where the neurodegeneration is associated with a condition selected from the group consisting of excitotoxicity, HIV-induced neuropathy, ischemia, subarachnoid hemorrhage, stroke, brain seizure, major heart attack, multiple infarction dementia, Alzheimer's Disease, Huntington's Disease, surgery-related brain damage and Parkinson's Disease. The administering step of this method can be any of a variety of administering procedures known to those of ordinary skill in the art, such as parenteral administration of a Calpain Inhibitor in a pharmaceutically acceptable carrier or oral administration of a Calpain Inhibitor in a form suitable for oral use. Parenteral administration is preferably by transdermal administration, subcutaneous injection, intravenous, intramuscular or intrasternal injection, intrathecal injection directly into the CNS or infusion techniques.

Detailed Description Text (149):

AA.sub.1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinedicarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (150):

AA.sub.2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinedicarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine,

S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (158):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipercolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (168):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipercolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (177):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipercolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (187):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipercolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH,

alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (188):

AA.sub.4 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of leucine, isoleucine, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (197):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (252):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (260):

AA.sub.1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2

--CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2  
--CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2  
--CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (261):

AA.sub.2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHET.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine.

Detailed Description Text (268):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHET.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine.

Detailed Description Text (276):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic add, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHET.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine.

Detailed Description Text (284):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHET.sub.2)-COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2

--CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2  
 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine.

Detailed Description Text (298):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, .alpha.-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, .alpha.-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (307):

AA.sub.1 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, .alpha.-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, .alpha.-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (308):

AA.sub.2 is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, .alpha.-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, .alpha.-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (316):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, .alpha.-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, .alpha.-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2

--CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (324):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, .alpha.-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipercolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)-COOH, .alpha.-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (332):

AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, .alpha.-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipercolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 --CHEt.sub.2)-COOH, .alpha.-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine;

Detailed Description Text (739):

As discussed above, therapeutics useful for influencing the function of cells within the CNS must cross the BBB to reach their targets within the CNS. Non-BBB permeant compounds might, in addition to the brain infusion techniques described above, be administered via intraventricular administration, but this also severely limits their usefulness in practice. In order to test the in vivo effectiveness of the Calpain Inhibitors to cross the BBB and become therapeutically useful, we tested the ability of intraperitoneal injection of the Calpain Inhibitors to protect against excitotoxic damage in vivo. Protection was measured by evaluating changes in behavior of rats after injection with kainate. These studies are shown in Example 8A.

Detailed Description Text (742):

Rats (male Sprague-Dawley, 200.+-.5 gms) were injected intraperitoneally with 12 mg/kg kainic acid in saline vehicle and ether 2001 .mu.l DMSO (dimethylsulfoxide) or 4.6 mg calpain inhibitor dissolved in the same volume of DMSO. The rats were observed for six hours following the injections and the kainate-induced behavioral symptoms and convulsions scored on a scale of 0-6 (0=no symptoms; 1=wet dog shakes; 2=salivation and chewing; 3=at least one convulsive episode; 4=repeated or sustained convulsions; 5=convulsions, including rearing and falling; 6=convulsions followed by death within the 6 hrs post injection).

Detailed Description Text (747):

Four days following the injection of kainate in the rats from Example 8A, the brains of the rats were removed and assayed for spectrin BDP's. Spectrin BDP's were assayed by homogenizing brain parts in 20 mM Tris pH=7.2, 0.32M sucrose, 501 .mu.M Ac-Leu-Leu-nLeu-H on ice. Homogenates were mixed 1:1 with 10% SDS, 5% .beta.-mercaptoethanol, 10% glycerol, 10 mM Tris pH=8.0, 0.5% bromophenolblue, heated to 95.degree. C., and subjected to electrophoresis in 41/2% polyacrylamide gels. The proteins in the gels were transferred to nitrocellulose and the spectrin and BDP's detected using a rabbit polyclonal anti-spectrin antibody and established immunodetection methods. The amount of spectrin and BDP's in each sample was

quantitated by densitometric scanning of the developed nitrocellulose.

Detailed Description Text (754):

For treatment of neurodegeneration, the Calpain Inhibitors can be administered orally, topically or parenterally. The term "parenteral" as used herein includes all non-oral delivery techniques including transdermal administration, subcutaneous injection, intravenous, intramuscular or intrasternal injection, intrathecal injection (directly into the CNS) or infusion techniques.

Detailed Description Text (757):

For injection, the therapeutic amount of the Calpain Inhibitors or their pharmaceutically acceptable salts will normally be made by subcutaneous injection, intravenous, intramuscular or intrasternal injection, or by intrathecal injection (directly into the brain). In order to provide a single day's dose with a single injection, the pharmaceutical compositions for parenteral administration will contain, in a single dosage form, from about 70  $\mu\text{g}$  to about 7 g of Calpain Inhibitor per dose of from about 0.5 ml to about 1 liter of carrier solution. In addition to the active ingredient, these pharmaceutical compositions will usually contain a buffer, e.g. a phosphate buffer that keeps the pH in the range from 3.5 to 7 and also sodium chloride, and can also contain mannitol or sorbitol for adjusting the isotonic pressure. In a preferred form of these compositions, DMSO or other organic solvent is added in order to assist the introduction of the Calpain Inhibitor across membranes.

Detailed Description Text (765):

A Neuroprotective Composition for Intravenous Injection

Detailed Description Text (772):

A first group of patients who are victims of head trauma is given 2 ml of the injectable composition of Example 9 intravenously within ten minutes of the time of injury. A second group of similarly matched patients does not receive the composition. The first group of patients exhibits markedly fewer and less severe outward symptoms of neurodegeneration, such as dementia, memory loss and paralysis.

CLAIMS:

11. The method of claim 10, wherein the administering step comprises transdermal administration, subcutaneous injection, intravenous, intramuscular or intrasternal injection, intrathecal injection directly into the CNS or infusion techniques.

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L8: Entry 26 of 29

File: USPT

May 17, 1988

DOCUMENT-IDENTIFIER: US 4745124 A

TITLE: Orally effective anti-hypertensive agents

Brief Summary Text (46):

A.sub.1 is (i) a residue of a compound having at least one carboxyl group and at least one alpha- or beta-amino or alpha-imino group, such as phenylalanine, alanine, tryptophan, tyrosin, isoleucine, leucine, histidine, valine, glycine, phenylglycine, beta-benzylaspartic acid, gamma-benzyl glutamic acid, S-benzyl-cysteine, O-benzyl-serine, O-benzyl tyrosine, O-benzyl threonine, betaphenyl serine, thyronine, beta-2-thienylserine, beta-2-thienylalanine, alpha-methyl-histidine, alpha-methyl tyrosine, alpha-methyl phenylalanine, alpha-methyl tryptophan, tyrosine having a halo, nitro, methoxy or hydroxy substituent, phenylalanine having a halo, nitro, amino or methoxy substituent, tryptophan having a fluoro, methyl or methoxy substituent, methionine, cysteine, arginine, omega-nitro-arginine, lysine, ornithine, aspartic acid, asparagine, glutamic acid, glutamine, homocysteine, penicillamine, norleucine, serine, beta-alanine, ethionine, homoserine, isoserine, norvaline, threonine, alpha-aminobutyric acid, alpha-aminoisobutyric acid, beta-cyclohexanyl-alanine, O-phosphothreonine, S-ethylcysteine, vinyl glycine, the alpha-methyl derivative of any of valine, leucine, isoleucine, cysteine, methionine, threonine, aspartic acid, glutamic acid, asparagine, glutamine, lysine and arginine; proline alpha-methyl proline, 3,4-dehydropoline, thiazolidine-4-carboxylic acid, cycloleucine, pyroglutamic acid, 1-amino-1-cyclopropane-carboxylic acid, 1-amino-1-cyclobutane carboxylic acid, 1-amino-1 cyclohexane carboxylic acid, or proline having a halo or hydroxy substituent; (ii) is in amide or imide linkage with R.sub.1 when R.sub.1 is acyl, and (iii) is in thioester linkage through a carboxyl group with -S-.

Brief Summary Text (88):

A sterile composition for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, and the like can be incorporated as required.

Detailed Description Text (667):

Rats (210-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I or II, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 80 ng of angiotensin I or angiotensin II in 20 .mu.l of 0.9 g % NaCl; an amount of antiotensin I or II sufficient to raise mean arterial blood pressure by 27-40 mm Hg. After the responsiveness of a given rat to angiotensins I and II was established, compound (I), at 2 or 5 mg/kg (drug dissolved in 0.5 ml of H.sub.2 O plus 10 .mu.l of 1N NaHCO.sub.3), was given via a stomach tube. At timed intervals, the effects of 80 ng of angiotensin I or angiotensin II on mean arterial blood pressure were tested. Results are shown in Table 17.

Detailed Description Text (678):

Rats (210-290 g body weight) were fasted overnight and then anesthetized with



intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I or II, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 160 ng of angiotensin I or 80 ng of angiotensin II in 20  $\mu$ l of 0.9 g % NaCl; an amount of angiotensin I or II sufficient to raise mean arterial blood pressure by 27-40 mm Hg. After the responsiveness of a given rat to angiotensins I and II was established, compound (B) at 10 mg (drug dissolved in 0.5 ml of H.sub.2 O plus 10  $\mu$ l of 1N NaHCO.sub.3), was given via a stomach tube. At timed intervals, the effects of 160 ng of angiotensin I or 80 ng of angiotensin II on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (685):

Rats (210-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/kg of angiotensin I in 20  $\mu$ l of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise mean arterial blood pressure by 39 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 17  $\mu$ mol/kg (drug dissolved in 0.15 ml of H.sub.2 O plus 10  $\mu$ l of 1N NaHCO.sub.3), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (688):

Anesthetized rats were prepared as described in Example 228. After the responsiveness of a given rat to angiotensin I was established, the named compound at 2  $\mu$ mol/kg, in a volume of 15  $\mu$ l of 0.01N sodium bicarbonate, was injected via a femoral vein. At timed intervals, the effects of angiotensin I, 400 ng/kg, on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (693):

Rats (190-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/kg of angiotensin I in 20  $\mu$ l of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise mean arterial blood pressure by 35 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 23  $\mu$ mol/kg (drug dissolved in 0.15 ml of H.sub.2 O plus 10  $\mu$ l of 1N NaHCO.sub.3), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (696):

Anesthetized rats were prepared as described in Example 231. After the responsiveness of a given rat to angiotensin I was established, the named compound, at 2  $\mu$ mol/kg, in a volume of 15  $\mu$ l of 0.01N sodium bicarbonate, was injected via a femoral vein. At timed intervals, the effects of angiotensin I, 400 ng/kg, on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (704):

Rats (210-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure

transducer connected to a polygraph. The rats were injected with 400 ng/kg of angiotensin I in 20  $\mu$ l of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise mean arterial blood pressure by 50 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 13.6  $\mu$ mole/kg (drug dissolved in 0.15 ml of H<sub>2</sub>O plus 10  $\mu$ l of 1N NaHCO<sub>3</sub>), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (709):

Rats (210-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/ml of angiotensin I in 20  $\mu$ l of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise mean arterial blood pressure by 37 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 20  $\mu$ mol/kg (drug dissolved in 0.15 ml of H<sub>2</sub>O plus 10  $\mu$ l of 1N NaHCO<sub>3</sub>), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I or on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (714):

Rats (210-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/ml of angiotensin I in 20  $\mu$ l of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise means arterial blood pressure by 38 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 20  $\mu$ mol/kg (drug dissolved in 0.15 ml of H<sub>2</sub>O plus 10  $\mu$ l of 1N NaHCO<sub>3</sub>), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (717):

Anesthetized rats were prepared as described in Example 239. The animals were administered the named compound via a femoral vein in 15  $\mu$ l of 0.01N sodium bicarbonate, after the control response to 400 ng/kg of angiotensin I was measured. Intravenous administration of the named compound resulted in a rapid decrease of blood pressure response to angiotensin I, 400 ng/kg, followed by a gradual rise to the pretreatment level of responsiveness. The time required for recovery of one half of the lost responsiveness to angiotensin I, following injection of the named compound, was designated  $t_{1/2}$ . For example, given the control response of 38 mm Hg, an initial decrease of 19 mm would constitute a reduction to 50% of the control response, and  $t_{1/2}$  would be the time required for the mean arterial blood pressure response to angiotensin I to reach 28.5 mm (75% of control). Results are shown for two dose levels:

Detailed Description Text (722):

Rats (210-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/ml of angiotensin I sufficient to raise mean arterial blood pressure by 25 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 20  $\mu$ mol/kg (drug dissolved in 0.15 ml of H<sub>2</sub>O plus 10  $\mu$ l of 1N NaHCO<sub>3</sub>), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown

below: 1

Detailed Description Text (725):

Anesthetized rats were prepared as described in Example 242. The named compound was administered intravenously via a femoral vein, at the stated dose, in 15 .mu.l of 0.01N sodium bicarbonate. The response to intravenous administration was a rapid decrease in responsiveness to Angiotensin I, 400 ng/kg, followed by a gradual recovery to the pretreatment level of responsiveness. The time required for recovery of one half the lost responsiveness to angiotensin I, following injection of the named compound, is designated t<sub>1/2</sub>. For example, given the control response of 35 mm Hg, an initial decrease of 17.5 mm would constitute a reduction to 50% of control, and t<sub>1/2</sub> would be the time required for the mean arterial blood pressure response to angiotensin I to increase to 26 mm (75% of control). Results are shown for the three dose levels:

Detailed Description Text (731):

Rats (190-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/ml of angiotensin I in 20 .mu.l of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise mean arterial blood pressure by 38 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 10 .mu.mol/kg (drug dissolved in 0.15 ml of H<sub>2</sub>O plus 10 .mu.l of 1N NaHCO<sub>3</sub>), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown below:

Detailed Description Text (737):

Rats (150-190 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/kg of angiotensin I in 20 .mu.l of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise mean arterial blood pressure by 45 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 10 .mu.mol/kg (drug dissolved in 0.15 ml of H<sub>2</sub>O plus 10 .mu.l of 1N NaHCO<sub>3</sub>), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown below:

**WEST****End of Result Set**

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L8: Entry 29 of 29

File: USPT

Jul 1, 1975

DOCUMENT-IDENTIFIER: US 3892852 A

TITLE: Pharmaceutical compositions containing cysteine derivatives

Brief Summary Text (4):

The present invention provides a pharmaceutical found: which 9.31 an 9.43 selected from L S-(3-hydroxypropyl)cysteine, L S-allyl cysteine, L S-allyl cysteine sulphoxide, L S-allyl-N-formylcysteine, L S-allyl-N-acetyl-cysteine, L S-(propen-1-yl)cysteine, L S-(buten-2-yl)cysteine, L S-propargyl cysteine, L S-methylcysteine, L S-ethylcysteine, L S-benzylcysteine and L S-(para-chlorobenzyl)cysteine and a pharmacologically acceptable diluent and/or excipient.

Brief Summary Text (20):S-ethylcysteine,Brief Summary Paragraph Table (15):

Batch 1 a 10% suspension of gum arabic Batch 2 200 mg/kg of LJ 84 + 100 mg/kg of LJ 537 Batch 3 200 mg/kg of LJ 559 (N-formyl-S-allyl- cysteine) Batch 4 200 mg/kg of LJ 560 (N-acetyl-S-allylcysteine) Batch 5 5 mg/kg of LJ 525 (S-propargylcysteine) Batch 6 200 mg/kg of LJ 526 (S-chlorobenzylcysteine) Batch 7 100 mg/kg of LJ 106 (S-methylcysteine) Batch 8 200 mg/kg of LJ 55 (S-benzylcysteine) Batch 9 200 mg/kg of LJ 81 (S-ethylcysteine) Batch 10 200 mg/kg of LJ 154 (S-allylcysteine sulphoxide)

Brief Summary Paragraph Table (17):

Examples 1 - 4 Lozenge Tablets 1) LJ 84 0.200 g Colloidal silica 0.020 g Lactose 0.080 g Excipient q.s for a tablet 2) LJ 84 0.100 g LJ 537 0.100 g Colloidal silica 0.020 g Lactose 0.080 g 0.300 g 3) LJ 106 0.250 g Colloidal silica 0.025 g Lactose 0.055 g Stearic acid 0.020 g 0.350 g 4) LJ 154 0.200 g Colloidal silica 0.010 g Microcrystalline cellulose 0.085 g Magnesium stearate 0.005 g 0.300 g Example 5 Capsule LJ 154 0.250 g Colloidal silica 0.010 g Talc 0.010 g 0.270 g Examples 6 - 8 Intravenously Injectable Solutions 6) LJ 84 0.250 g Sodium bicarbonate to give pH 6.8 0.020 g Sodium chloride 0.050 g Distilled water to make 10 ml 7) LJ 84 0.100 g LJ 537 0.100 g Sodium chloride 0.050 g Sodium bicarbonate to give pH 6.8 Distilled water to make 10 ml 8) LJ 106 0.100 g Sodium bicarbonate to give pH 6.8 Distilled water to make 10 ml

**CLAIMS:**

3. The method of reducing atheromatic deposits and plasma cholesterol levels in a patient suffering from an atheromatic disease or a disorder of the lipid metabolism which comprises administering to said patient a daily dose of from 200 mg to 3.0 gram of an L S-substituted cysteine selected from the group consisting of L S-(3-hydroxypropyl)cysteine, L S-allyl cysteine, L S-allyl cysteine sulphoxide, L S-allyl-N-formylcysteine, L S-allyl-N-acetylcysteine, L S-propargyl cysteine, L S-methyl cysteine, L S-ethylcysteine, L S-benzylcysteine and L S-(parachlorobenzyl)cysteine.

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L8: Entry 22 of 29

File: USPT

Apr 26, 1994

DOCUMENT-IDENTIFIER: US 5306824 A

TITLE: Biotinylated isocoumarins

Detailed Description Text (14):

wherein AA is a side chain blocked or unblocked amino acid with the L configuration, D configuration, or no chirality at the .alpha.-carbon selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipecolic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CH<sub>2</sub>.sub.2)--COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, or hexafluoroleucine,

Detailed Description Text (40):

It is known that in vitro activity of elastase inhibitors correlates with in vivo activity in animal models of emphysema and inflammation (Otterness et al., editor, *Advances in Inflammation Research*, Vol. 11, Raven Press 1986, and this article is incorporated herein by reference). Prophylactic administration of an inhibitor of elastase significantly diminishes the extent of elastase-induced emphysema (Kleinerman et al., *Am. Rev. Respir. Dis.* 121, pp 381-387 (1980); Lucey et al., *Eur. Respir. J.* 2, pp 421-427 (1989)). Thus the novel inhibitors described here should be useful for the treatment of emphysema and inflammation. Elastase inhibitors have been used orally, by injection or by instillation in the lungs in animal studies (Powers, *Am. Rev. Respir. Dis.*, 127, s54-s58 (1983); Powers and Bengali, *Am. Rev. Respir. Dis.* 134, pp 1097-1100 (1986) and these two articles are incorporated herein by reference). The inhibitors described above can be used by any of these routes.

Detailed Description Text (41):

For treatment of inflammation, the compounds of Formula (I) may be administered orally, topically or parenterally. The term parenteral as used includes subcutaneous injection, intravenous, intramuscular, intrasternal injection or infusion techniques. The dosage depends primarily on the specific formulation and on the object of the therapy or prophylaxis. The amount of the individual doses as well as the administration is best determined by individually assessing the particular case.

Detailed Description Text (43):

For injection, the therapeutic amount of the compounds of Formula (I) or their pharmaceutically acceptable salts will normally be in the dosage range from 0.2 to 140 mg/kg of body weight. Administration is made by intravenous, intramuscular or subcutaneous injection. Accordingly, pharmaceutical compositions for parenteral administration will contain in a single dosage form about 10 mg to 7 gms of compounds of Formula (I) per dose. In addition to the active ingredient, these pharmaceutical compositions will usually contain a buffer, e.g. a phosphate buffer which keeps the pH in the range from 3.5 to 7 and also sodium chloride, mannitol or sorbitol for adjusting the isotonic pressure.

## CLAIMS:

3. A compound of the formula: ##STR6## or a pharmaceutically acceptable salt thereof, wherein Z is selected from the group consisting of H, halogen, C.sub.1-6 alkyl, C.sub.1-6 fluorinated alkyl, C.sub.1-6 alkyl substituted with R.sup.1, C.sub.1-6 fluorinated alkyl substituted with R.sup.1, C.sub.1-6 alkoxy, C.sub.1-6 fluorinated alkoxy, C.sub.1-6 alkoxy substituted with R.sup.1, C.sub.1-6 fluorinated alkoxy substituted with R.sup.1, C.sub.1-6 alkyl with a phenyl group attached to the alkyl group, C.sub.1-6 alkoxy with a phenyl group attached to the alkoxy group, C.sub.1-6 alkyl with an attached phenyl group substituted with R.sup.2, C.sub.1-6 alkyl with an attached phenyl group disubstituted with R.sup.2, C.sub.1-6 alkoxy with an attached phenyl group substituted with R.sup.2, C.sub.1-6 alkoxy with an attached phenyl group disubstituted with R.sup.2,

wherein R.sup.2 represents halogen, COOH, OH, CN, NO.sub.2, NH.sub.2, C.sub.1-6 alkyl, C.sub.1-6 alkoxy, C.sub.1-6 alkylamine, C.sub.1-6 dialkylamine, C.sub.1-6 alkyl-O--CO--, C.sub.1-6 alkyl-O--CO--NH--, or C.sub.1-6 alkyl-S--,

wherein R.sup.1 represents halogen, COOH, OH, CN, NO.sub.2, NH.sub.2, C.sub.1-6 alkoxy, C.sub.1-6 alkylamine, C.sub.1-6 dialkylamine, C.sub.1-6 alkyl-O--CO--, C.sub.1-6 alkyl-O--CO--NH--, C.sub.1-6 alkyl-S--, or tosylamino,

wherein R is the side chain of a side chain blocked or unblocked amino acid residue selected from the group consisting of alanine, valine, leucine, isoleucine, proline, methionine, methionine sulfoxide, phenylalanine, tryptophan, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, phenylglycine, beta-alanine, norleucine, norvaline, alpha-aminobutyric acid, epsilon-aminocaproic acid, citrulline, hydroxyproline, ornithine, homoarginine, sarcosine, indoline 2-carboxylic acid, 2-azetidinecarboxylic acid, pipercolinic acid (2-piperidine carboxylic acid), O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, NH.sub.2 --CH(CH.sub.2 CHEt.sub.2)--COOH, alpha-aminoheptanoic acid, NH.sub.2 --CH(CH.sub.2 -1-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -2-naphthyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclohexyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopentyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclobutyl)-COOH, NH.sub.2 --CH(CH.sub.2 -cyclopropyl)-COOH, trifluoroleucine, and hexafluoroleucine,

wherein n=1-6,

wherein T represents --NH--, --O--, or --S--,

Y is selected from the group consisting of H, halogen, trifluoromethyl, methyl, OH and methoxy.

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L8: Entry 28 of 29

File: USPT

Apr 3, 1984

DOCUMENT-IDENTIFIER: US 4440788 A

TITLE: Cysteine derivatives

Brief Summary Text (18):

S-methylcysteinamide, S-methylcysteine methylamide, S-methylcysteine ethylamide, S-ethylcysteine dimethylamide, N-(S-methylcysteinyl)-azetidine, N-(S-methylcysteinyl)pyrrolidine, S-ethylcysteinamide, S-ethylcysteine methylamide, S-ethylcysteine ethylamide, S-ethylcysteine propylamide, S-ethylcysteine butylamide, S-ethylcysteine pentylamide, S-ethylcysteine hexylamide, S-ethylcysteine dimethylamide, S-ethylcysteine methylethylamide, S-ethylcysteine diethylamide, N-(S-ethylcysteinyl)-azetidine, N-(S-ethylcysteinyl)-pyrrolidine, N-(S-ethylcysteinyl)-piperidine, etc.

Brief Summary Text (51):

The form in which the pharmaceutical compositions of this invention may be provided includes powders, granules, tablets, sugar-coated tablets, pills, capsules, solutions, etc. for oral administration, as well as suppositories, suspensions, solutions, emulsions, ampules, injections, etc. for parenteral administration. Of course, a combination of these may be employed.

Brief Summary Text (57):

Suitable vehicles for injection include sterilized water, lidocaine hydrochloride solutions (for intramuscular injection), physiological saline, glucose, liquids for intravenous injection and electrolyte solutions (for intravenous injection and drip infusion). These injections may usually be prepared so as to contain 0.5% to 20%, preferably 1% to 10% by weight of a compound of this invention.

Detailed Description Text (36):

In 80 ml of methanol was suspended 4.47 g (0.03 mole) of S-ethylcysteine and 4.28 g (0.036 mole) of thionyl chloride was then added dropwise to the suspension under stirring and ice cooling. The reaction mixture was stirred for about 3 hours and then allowed to stand overnight and the resulting homogenous solution was concentrated. To the residue was added 100 ml of chloroform and the solution was washed with aqueous 5% sodium bicarbonate and dried over anhydrous magnesium sulfate. The chloroform was then distilled off in vacuo to give an oil which is S-ethylcysteinamide. To the oil was added 100 ml of methanol and ammonia gas was passed through the resulting solution under cooling with ice-water until the solution was saturated with ammonia. The solution was then allowed to stand for 2 days as it was. After the methanol and ammonia were distilled off in vacuo, another 80 ml aliquot of methanol was added and hydrogen chloride gas was passed through the resulting solution.

Detailed Description Text (37):

The solution was concentrated and the resulting crystals were collected by filtration and dried to give 1.88 g of S-ethylcysteinamide hydrochloride, 34% yield based on S-ethylcysteine, m.p. 212.degree.-213.degree. C.

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L8: Entry 27 of 29

File: USPT

Mar 29, 1988

DOCUMENT-IDENTIFIER: US 4734420 A

TITLE: Anti-hypertensive agents

Brief Summary Text (41):

A is methionine, cysteine, arginine, .omega.-nitro-arginine, lysine, ornithine, aspartic acid, asparagine, glutamic acid, glutamine, homocysteine, penicillamine, norleucine, serine, .beta.-alanine, ethionine, homoserine, isoserine, norvaline, threonine, .alpha.-aminobutyric acid, .alpha.-aminoisobutyric acid, .beta.-cyclohexanyl-alanine, O-phosphothreonine, S-ethylcysteine, vinyl glycine or the .alpha.-methyl derivative of valine, leucine, isoleucine, cysteine, methionine, threonine, aspartic acid, glutamic acid, asparagine, glutamine, lysine or arginine, the .alpha.-amino group or .beta.-amino group of .beta.-alanine thereof being in amide linkage respectively with R, and the carboxyl group thereof being in thioester linkage with S;

Brief Summary Text (109):

Sterile composition for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, and the like can be incorporated as required.

Detailed Description Text (309):

Rats (190-290 g body weight) were fasted overnight and then anesthetized with intraperitoneal pentobarbital, 50-60 mg/kg. Tracheostomy was performed and the animals were ventilated mechanically. A cannula was inserted into a femoral vein for injection of angiotensin I, and a second cannula was inserted into a common carotid artery for direct measurement of arterial blood pressure. Heparin, 1,000 units, was injected via the femoral vein to prevent coagulation. Blood pressure was measured with a pressure transducer connected to a polygraph. The rats were injected with 400 ng/ml of angiotensin I in 20 ul of 0.9 g % NaCl; an amount of angiotensin I sufficient to raise mean arterial blood pressure by 38 mm Hg. After the responsiveness of a given rat to angiotensin I was established, the named compound at 10 umol/kg (drug dissolved in 0.15 ml of H.sub.2O plus 10 ul of 1N NaHCO.sub.3), was given via a stomach tube. At timed intervals, the effects of 400 ng/kg of angiotensin I on mean arterial blood pressure were tested. Results are shown below:

## CLAIMS:

1. A new compound having the general formula

R-A-S-Z

wherein

R is hydrogen, formul, acetyl, propanoyl, butanoyl, phenylacetyl, phenylpropanoyl, benzoyl, cyclopentanecarbonyl, tert-butyloxycarbonyl, cyclopentanecarbonyl-L-lysyl, pyro-L-glutamyl-L-lysyl, L-arginyl, L-lysyl or pyro-L-glutamyl;

A is a divalent moiety derived from methionine, cysteine, arginine, .omega.-nitro-arginine, lysine, ornithine, aspartic acid, asparagine, glutamic acid,



glutamine, homocystein, penicillamine, norleucine, serine, .beta.-alanine, ethionine, homoserine, isoserine, norvaline, threonine, .alpha.-aminobutyric acid, .alpha.-aminoisobutyric acid, cyclohexanyl-alanine, O-phosphothreonine, S-ethylcysteine, vinyl glycine or an .alpha.-methyl derivative of any of valine, leucine, isoleucine, cysteine, methionine, threonine, aspartic acid, glutamic acid, asparagine, glutamine, lysine or arginine, wherein the .beta.-amino group of the moiety derived from .beta.-alanine or the .alpha.-amino group of the moiety derived from each other named amino acid is in amide linkage with R when R is acyl and such moiety forms a primary amine group with R when R is H and the carboxyl group of said moiety is in thioester linkage with S;

S is a sulfur atom joined in thioester linkage to A; and Z is selected from the following: ##STR69## wherein (i) R.sub.1 and R.sub.1', are each hydrogen or halogen, and R.sub.2 and R.sub.3 are each hydrogen, lower alkyl or trifluoromethyl provided that only one of R.sub.2 and R.sub.3 may be trifluoromethyl and further provided that at least one of R.sub.1, R.sub.1', R.sub.2 and R.sub.3 must be halogen or trifluoromethyl;

(ii) R.sub.23 is hydrogen or lower alkyl and

(iii) m is 0 or 1; ##STR70## wherein (i) R.sub.4 and R.sub.5 are each hydrogen, lower alkyl or phenyl-lower alkylene;

(ii) n is 1, 2 or 3;

(iii) R.sub.6 is hydrogen or hydroxy or when n is 2, R.sub.6 may also be halogen and

(iv) m and R.sub.23 are as stated in II above; ##STR71## wherein (i) R.sub.7 is hydrogen, lower alkanoyl or amino (imino)methyl;

(ii) p is 0 or an integer of from 1 to 4;

(iii) R.sub.25 is hydrogen but when m is 1, p is 0, R.sub.4 is hydrogen and R.sub.7 is lower alkanoyl, R.sub.25 may also be lower alkyl;

(iv) R.sub.8 is selected from hydrogen, lower alkyl and hydroxy lower alkylene and R.sub.9 is selected from hydrogen, lower alkyl, phenyl, phenyl-lower alkylene, hydroxy-lower alkylene, hydroxy phenyl-lower alkylene, mercapto-lower alkylene, lower alkyl-thio-lower alkylene, imidazolyl-lower alkylene, indolyl-lower alkylene, carbamoyl-lower alkylene and carboxy-lower alkylene but R.sub.8 and R.sub.9 may together constitute a (CH.sub.2).sub.v bridge wherein v is 3 or 4, thus forming a 5 or 6-membered ring with the N and C to which R.sub.8 and R.sub.9 are respectively attached and in such instance when v is 3 one hydrogen of (CH.sub.2).sub.v may be replaced by OH or halogen and when v is 4, one such hydrogen may be replaced by OH;

(v) m and R.sub.23 are each as defined in II above, and

(vi) R.sub.4 is as defined in III above, provided further however, that m and p may not both be 0, ##STR72## wherein (i) R.sub.10 is hydrogen or lower alkyl;

(ii) R.sub.11 is hydrogen, lower alkyl or lower alkanoyl;

(iii) X is O or S;

(iv) m and R.sub.23 are as stated in II above, and

(v) R.sub.8, R.sub.9 and p are as stated in IV above. ##STR73## wherein (i) R.sub.12 is selected from carboxy, lower alkoxycarbonyl, carbamoyl, N-substituted carbamoyl and cyano;

(ii) m and R.sub.23 are as stated in II above; and

(iii) R.sub.8, R.sub.9 and p are as stated in IV above. ##STR74## wherein (i) R.sub.13 is hydrogen, lower alkyl or phenyl-lower alkylene:

- ✓ (ii) R.sub.14 is selected from hydrogen, lower alkyl, phenyl-lower alkylene, hydroxy-lower alkylene, amino-lower alkylene, guanidino-lower alkylene, imidazolyl-lower alkylene, indolyl-lower alkylene, mercapto-lower alkylene, lower alkyl-thio-lower alkylene, carbamoyl-lower alkylene and carboxy-lower alkylene;
- (iii) R.sub.4 and R.sub.5 are each as stated in III above; and
- (iv) q is 0, 1 or 2; ##STR75## wherein (i) R.sub.15 and R.sub.16 are each hydrogen, lower alkyl, phenyl or phenyl-lower alkylene;
- (ii) r is 0, 1 or 2;
- (iii) s is 1, 2 or 3;
- (iv) R.sub.17 is hydrogen, hydroxy or lower alkyl and when s is 2, R.sub.17 may also be halogen;
- (v) R.sub.24 is hydroxy, amino or lower alkoxy; ##STR76## wherein (i) R.sub.18 is hydrogen or lower alkyl;
- (ii) R.sub.19 and R.sub.20 are each lower alkyl and may together constitute a (CH.sub.2).sub.w bridge wherein w is 4, to form a ring of 5-carbons with the carbon to which they are attached;
- (iii) R.sub.21 is hydrogen or lower alkyl and may constitute with R.sub.19 a (CH.sub.2).sub.x bridge wherein x is 3, to form a five-membered ring with the N and C to which they are respectively attached; ##STR77## wherein (i) R.sub.22 is hydrogen or lower alkyl;
- (ii) t is 0 or 1; and
- (iii) R.sub.26 is selected from ##STR78## wherein u is 0 or 1 and R.sub.23 is as defined for formula II above. ##STR79## wherein (i) z is 2 or 3;
- (ii) R.sub.10 is as stated in V above; and
- (iii) R.sub.3 is as stated in II above.

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((S-METHYL-L-CYSTEINE).USPT,PGPB,JPAB,EPAB,DWPI,TDBD.	90

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result set*DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ*

<u>L9</u>	s-methyl-l-cysteine	90	<u>L9</u>
<u>L8</u>	17 and 14	29	<u>L8</u>
<u>L7</u>	s-alkylthiol\$5 or s-ethylcysteine or s-methylcysteamine or s-ethylcysteamine or s-ethylglutathione or s-methylglutathione or s-methylcoenzyme a or s-ethylcoenzyme	57	<u>L7</u>
<u>L6</u>	14 same 13	1	<u>L6</u>
<u>L5</u>	14 and 13	176	<u>L5</u>
<u>L4</u>	parenternally\$5 or parenternal\$5 or inject\$6 or injection\$5 or intravenous\$5 intraven\$5	940338	<u>L4</u>
<u>L3</u>	11 or 12	314	<u>L3</u>
<u>L2</u>	s-methyl cysteine or s-methyl-l-cysteine	212	<u>L2</u>
<u>L1</u>	s-methylcysteine	116	<u>L1</u>

END OF SEARCH HISTORY

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=> s s-methylcysteine/cn

L1 1 S-METHYLCYSTEINE/CN

=> d

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RN 1187-84-4 REGISTRY

CN L-Cysteine, S-methyl- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Alanine, 3-(methylthio)-, L- (8CI)

OTHER NAMES:

CN (-)-S-Methyl-L-cysteine

CN 3-(Methylthio)alanine

CN L-S-Methylcysteine

CN S-Methyl-(R)-cysteine

CN S-Methyl-L-cysteine

CN **S-Methylcysteine**

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CI COM

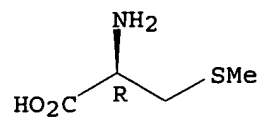
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